

### **REMARKS**

Claims 1-6 have been cancelled. Claims 7-8 have been amended. New claims 9-16 are added. Claims 7-16 are now pending in this application.

Support for the claim amendments is as follows. The amendment to claims 7-8 is supported by original claim 4 and page 5, lines 15-16 of the present specification.

The limitation "caused by spinal cord injury or nerve trauma" in claim 9 is based on original claim 6.

The limitation "recovering a nervous function" in claim 10 is supported by page 15, paragraph 2 of the present specification.

Support for amendments to claim 11 is as follows:

Support for "decrease of a nervous function" is found on page 15, paragraph 2.

Support for "demyelination" is found on page 15, paragraph 3.

Support for "edema in white matter" is found on page 14, lines 4-6.

Support for "reduction in axon number" is found on page 15, paragraph 3.

Support for "tissue damage" is found on page 15, paragraph 3.

The limitation "hyaluronic acid tetrasaccharide" in claims 11-16 is based upon original claim 5.

No new matter is added herewith. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

#### **Rejections under 35 U.S.C. § 102(b)**

Claims 1-6 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Seikagaku Corporation (WO 02/04471A1).

Claims 1, 2, and 6 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Atsuta, et al. (JP 11-140103A).

The above grounds of rejection are rendered moot by Applicants' cancellation of claims 1-6.

#### **Rejection under 35 U.S.C. § 103(a)**

Claims 7-8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Atsuta, et al. (JP 11-140103A).

The Office Action asserts that Atsuka, et al. disclose a low molecular weight hyaluronic acid which can be used to treat nerve damage and that Atsuka, et al differ from the claimed method only in not exemplifying the use of low molecular weight hyaluronic acid.

The claims have been amended to recite “a hyaluronic acid oligosaccharide...wherein the hyaluronic acid oligosaccharide is selected from hyaluronic acid disaccharide to hyaluronic acid 50-saccharide”. Atsuka, et al. do not teach “a hyaluronic acid oligosaccharide” as claimed as discussed further below.

Atsuta, et al. disclose a perfusion solution for spinal cord comprising an aqueous solution of hyaluronic acid, the hyaluronic acid used in Atsuta, et al. has a molecular weight of 500,000 to 4,000,000 and, as stated in the CAPLUS abstract provided by the Examiner, a weight average molecular weight of 890,000.

In contrast, the present claims have been amended to recite “a hyaluronic acid oligosaccharide...wherein the hyaluronic acid oligosaccharide is selected from hyaluronic acid disaccharide to hyaluronic acid 50-saccharide” corresponding to a molecular weight of about 400 to 10000. As stated in the specification, low-molecular weight HA is preferred (page 4, line 19) and low molecular weight is further defined on pages 4-5. It is clearly stated that a “molecule having an average molecular weight of more than 1,000 kD is not recognized as a molecule having a “low-molecular weight” in the art” (present specification, page 5, paragraph 2) and that “HA oligosaccharide is extremely preferable” (present specification, page 5, paragraph 3). The specification teaches that “HA oligosaccharide includes HA disaccharide to HA 50-saccharide” (page 5, paragraph 4). Accordingly, Atsuka, et al. do not teach the method as presently claimed and, in fact, teach away from the claimed invention by suggesting the use of high molecular weight HA rather than “hyaluronic acid oligosaccharide” as claimed.

Furthermore, by using hyaluronic acid oligosaccharide having the above-described molecular size, the presently claimed method produces unexpected effects such as recovery of nervous function, suppression of a decrease in nervous function, demyelination and edema in white matter, and reduction in axon number or tissue damage (see present specification, pages

14-15 “(5) Evaluation from praxiologic viewpoint (severely injured model (II))”. Such effects could not have been predicted based upon the disclosure of Atsuka, et al.

Indeed, Atsuka, et al. describe that undesirable effects such as deterioration of inflammation, bleeding and allergy may be caused by use of hyaluronic acid having molecular weight outside of the 500,000 to 4,000,000 range (Atsuka, et al. (JP 11-140103), paragraph 0023). Accordingly, Atsuka, et al. clearly teach away from the claimed method which is directed to “hyaluronic acid oligosaccharide...wherein the hyaluronic acid oligosaccharide is selected from hyaluronic acid disaccharide to hyaluronic acid 50-saccharide”. By following the teaching of Atsuka, et al. one of ordinary skill in the art would never use such a low molecular weight hyaluronic acid in view of the undesirable effects taught by Atsuka, et al.

Contrary to the disclosure of Atsuka, et al., hyaluronic acid disaccharide to hyaluronic acid 50-saccharide have a superior effect compared to hyaluronic acid having larger molecular weight as shown in the attached Declaration under 37 C.F.R. § 1.132 of Akiomi Tanaka (Tanaka Declaration). The Tanaka Declaration compares effects of HA4 and HA (900kDa) on spinal cord injury in a model animal system. HA4 is hyaluronic acid tetrasaccharide which corresponds to the claimed invention, and HA (900kDa) is hyaluronic acid having larger molecular weight within the range taught by Atsuka, et al. (JP 11-140103).

As shown in the result of the BBB test (see Figure on page 3 of Tanaka Declaration), HA4 had a remarkable effect of recovering hind limb-motor function, but HA (900kDa) did not have such an effect. The effects of HA (900kDa) were similar to the saline control.

Furthermore, the perfusion solution for spinal cord disclosed in Atsuka, et al. is a solution to be perfused into an injury site upon surgery or treatment of a spinal cord injury (paragraph 0001), and is used for preventing second denaturation including microbleeding and ischemic change by washing away second mediators (toxic substances) accumulated after spinal cord injury (paragraph 0055). On the other hand, in the presently claimed invention, hyaluronic acid disaccharide to hyaluronic acid 50-saccharide (which includes hyaluronic acid tetrasaccharide of the Tanaka Declaration) is administered into a body via injection, nasal administration, oral administration, percutaneous administration, inhalation, instillation or the like (see present specification, page 7, last paragraph), and is used for inhibition of progression of nerve damage (prevention of deterioration), remedy or treatment of symptoms.

In summary, the presently claimed invention differs from the teaching of Atsuka, et al. in molecular size of hyaluronic used, formulation, purpose and effect. Additionally, the Tanaka Declaration demonstrates the unexpected benefits of using "hyaluronic acid oligosaccharide...wherein the hyaluronic acid oligosaccharide is selected from hyaluronic acid disaccharide to hyaluronic acid 50-saccharide" according to the claimed invention as measured in a model system which was unexpected in view of the cited reference.

In view of Applicants' amendments, arguments and the Tanaka Declaration, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

**No Disclaimers or Disavowals**

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

**Co-Pending Applications of Assignee**

Applicant wishes to draw to the Examiner's attention to the following co-pending applications of the present application's assignee (Entry in **BOLD** is the present application).

Serial Number	Title	Filed
10/262526	GENES FOR TRANSFECTION INTO BONY TISSUES	30-Sep-2002
11/595410	SULFOTRANSFERASE AND DNA ENCODING THE ENZYME	09-Nov-2006
10/482678	PROCESS FOR PRODUCTION OF SUGAR OXAZOLINE DERIVATIVES	30-Dec-2003
10/546223	BIOLOGICALLY ACTIVE PEPTIDE AND AGENT CONTAINING THE SAME	18-Aug-2005
<b>10/550998</b>	<b>THERAPEUTIC AGENT FOR NERVE DAMAGE</b>	<b>24-Oct-2005</b>
10/557652	SULFOTRANSFERASE INHIBITOR	21-Nov-2005

10/563540	METHOD OF DETECTING CANCER	22-Dec-2005
11/658103	MUTANT GLYCOPROTEIN RESISTANT TO MODIFICATION WITH ASPARAGINE-LINKED SUGAR CHAIN	22-Jan-2007

**CONCLUSION**

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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